Subcellular fractionation revealed CaT1 was localized to membrane fractions and enriched in purified zymogen granule (ZG) membranes. CaT1 was insensitive to carbonate (pH 11) washing, indicating it is an integral membrane protein. In screening for potential CaT1 interactions with known (ZG) membrane proteins, a strong association was detected with the co-chaperone molecule, cysteine string protein (CSP). CSP functions in nerves by co-activating the chaperone activity of heat shock protein 70. The interaction between CSP and CaT1 was demonstrated by pull-down assays in ZG lysates using a GST-CSP fusion construct, and confirmed by coIP of CaT1 with CSP antibodies. In both the GST-CSP pull-downs and coIPs, CaT1 was quantitatively depleted from lysates by CSP precipitation, indicating a strong interaction between the proteins. In nerve and endocrine cells, CSP modulates Ca^{2+} influx by associating with voltage-regulated Ca^{2+} channels. As digestive epithelia do not express voltage-regulated Ca^{2+} channels, we propose that CSP has and analogous function in digestive epithelia to modulate CaT1-mediated Ca^{2+} entry at the apical membrane.

339.8

Relationship among proliferation, p27, differentiation and apoptosis measured by colocalization in the same cell as a function of carcinogen administration

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Colon cancer develops from cellular damage leading to an imbalance in the equilibrium among proliferation, differentiation and apoptosis. This study measured these variables in the same cell to determine how the balance is altered in response to azoxymethane (AOM) during the initiation stage of colon cancer. Rats (n=36) were injected with AOM and terminated 12, 24 or 48 h later. Saline-injected rats served as controls. Proliferation (Ki-67), p27, differentiation (lectin) and apoptosis (TUNEL) were measured in the same cell within a crypt to strengthen our ability to understand the coordination of cell cycle as a function of carcinogen. Proliferative index was lowest at 12 h and returned to the same level by 48 h ($p=0.0001$). Crypt height decreased 24 h post AOM injection ($p=0.0017$). Differentiation was enhanced ($p=0.0144$) and apoptosis was maximized ($p=0.0001$) 24 h after AOM injection. There was a positive correlation between proliferation and p27 ($r=0.37$, $p=0.0096$), and between p27 and differentiation ($r=0.25$, $p=0.0418$). The parallel relationship of p27 (a cell cycle inhibitor) and proliferation to carcinogen injection may be a protective response that leads to enhanced differentiation and subsequent apoptosis. These results demonstrated that colonocytes actively respond to carcinogen insult to reduce the propagation of mutated cells and to remove the damaged cells.
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HUMAN DIETARY STUDIES ON CANCER (340.1-340.8)

340.1

Are Dietary Phytate (IP6) and Fecal Phytate Related to Colorectal Polyp Formation and Recurrence?

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Colorectal adenomatous polyps are recognized as precursor lesions of colorectal cancer. A sub-set of 60 subjects entered into The Polyp Prevention Trial (PPT) initiated by the National Cancer Institute in 1994. It assessed the influence of diet on recurrence of colonic polyps in patients following an initial colonoscopy & subsequent removal of all polyps. Participants agreed to a follow-up colonoscopy, one, and four years after entry into the trial. Half of the randomized participants remained on their usual diet (Control Group), and half were provided instruction for diet intervention (Intervention Group). After 9-12 months of a daily dietary pattern low in fat (20% kcal), high fiber (18 g/1000 kcal) & 5-8 servings of fruits & vegetables, participants produced a 72-hr stool collection at home. Because of increased dietary fiber (and thus phytate) by both Groups, the phytate content of the diet and stools were examined. Four-Day Food Records & Food Frequency Questionnaires were calculated for phytate; stool phytate was analyzed by HPLC. Dietary phytate values ranged from 320 to 1121 mg/day. Fecal phytate values ranged from 0.053 to 109.4 mg/g feces. As dietary phytate increased, stool phytate increased as well. Humans have no enzyme to hydrolyze phytate in the GI tract. From preliminary data, subjects consuming diets high in phytate were non-polyp formers throughout the remaining two years of the study.
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340.2

Dietary differences among categories of dietary supplement use in colorectal cancer survivors and a comparison population

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Data from the North Carolina Strategies to Improve Diet, Exercise, and Screening study (n=727) were used to identify and describe categories of dietary supplement use and evaluate how these categories are associated with vegetable and fruit intake. Five nonoverlapping categories were created and descriptive statistics were used to examine demographic differences. Least-squares means were calculated for each of the vegetable and fruit measures. Logistic regression was performed to calculate adjusted odds ratios to examine associations among the dietary supplement use categories and the vegetable and fruit measures. Demographic profiles and dietary intake varied among dietary supplement use categories. Persons in Category 1 (multivitamin and single supplements) and Category 2 (nonvitamin/nonmineral products) were more likely to be consuming more vegetables, and higher quality vegetables and fruits, than Category 5 (no dietary supplements), while Category 4 (multivitamins only) had patterns that were more consistently similar to Category 5. Study participants exhibited dietary supplement use patterns which were associated with differences in vegetable and fruit consumption. Simply characterizing individuals as using/not using dietary supplements will not capture critical demographic and dietary differences and will likely further cloud investigations of diet/cancer relationships.

340.3

Effect of estimated renal net acid excretion (NAE) on bladder cancer risk in a cohort of male smokers

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In several animal and human studies, low urine pH (< 6.0) has been associated with elevated levels of unconjugated aromatic amines in urine and arylamine-DNA adducts in bladder epithelial cells. Urine pH, which is largely influenced by diet and weight, may therefore be an important risk factor for bladder cancer. A calculation model that utilizes dietary data and anthropometric information to estimate renal net acid excretion (NAE) has been previously developed. Two validation studies have shown that the NAE estimate correlates reasonably well with actual urine pH levels. We investigated the relationship between estimated renal NAE and bladder cancer risk within the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort. At baseline, 27,111 male smokers 50–69 years old completed a dietary questionnaire that assessed usual frequency of consumption and portion sizes for the previous year. Data on height, weight, and history of smoking were also ascertained. 344 incident bladder cancer cases were identified during up to 14 years of follow-up. The multivariate relative risks for bladder cancer were 1.0, 1.23, 0.81, 0.92, and 1.06 (95% confidence interval = 0.76-1.48) for increasing NAE quintiles (p trend = 0.71). There was no apparent effect modification by smoking, fluid intake, age, or body mass index. These findings do not support the hypothesis that acidic urine enhances bladder cancer risk in male smokers.
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